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| (21) International Application Number: PCT/SE96/00161 (22) International Filing Date: 9 February 1996 (09.02.96) (30) Priority Data: 9500478-4 9 February 1995 (09.02.95) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): LUNDBERG, Per, Johan [SE/SE]; Torsgatan 6, S-431 38 Mölndal (SE). LÖVGREN, Kurt [SE/SE]; Violinvägen 2D, S-435 44 Mölnlycke (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE). | | (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: NEW PHARMACEUTICAL FORMULATION AND PROCESS (57) Abstract A new oral pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compounds and optionally pharmaceutical excipients having a water soluble separating layer and an enteric coating layer. The core material as such is alkaline reacting and the separating layer between the alkaline reacting core material and the enteric coating layer is formed in situ as a water soluble salt between the alkaline reacting compound(s) and the enteric coating polymer. The invention also describes a new efficient process for the manufacture of such a dosage form comprising two functionally different layers in one manufacturing step, and its use in medicine. | | |

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NEW PHARMACEUTICAL FORMULATION AND PROCESS

Field of the invention

5 The present invention refers to new pharmaceutical formulations comprising acid labile heterocyclic compounds with gastric inhibitory effect, in the following referred to as proton pump inhibitors. The new formulations are intended for oral use. Furthermore, the present invention refers to a new method for the manufacture of such a formulation and, the use of the new formulations in medicine.

10

Background of the invention

The proton pump inhibitors are for example compounds of the general formula I

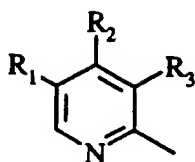
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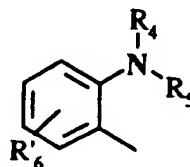
wherein

Het₁ is

20

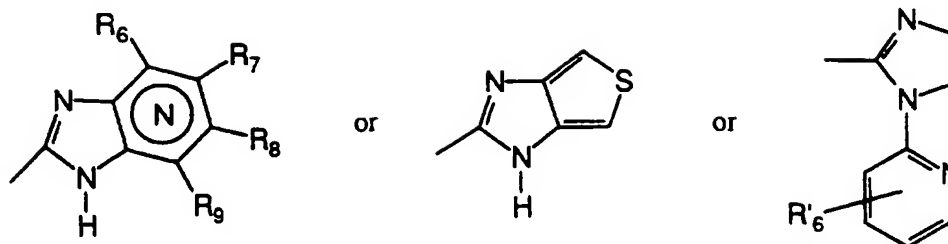


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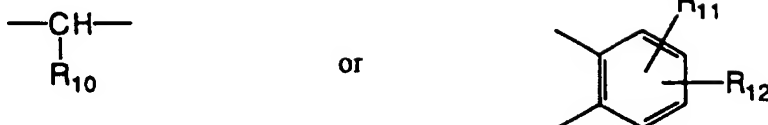


25

Het₂ is



X =



5 wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

10 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

15

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

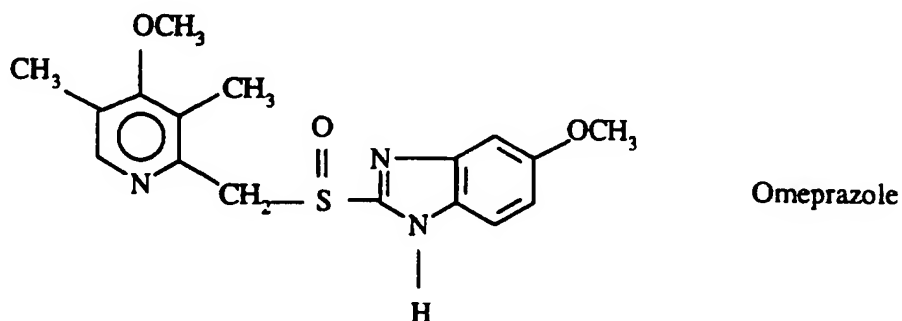
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R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

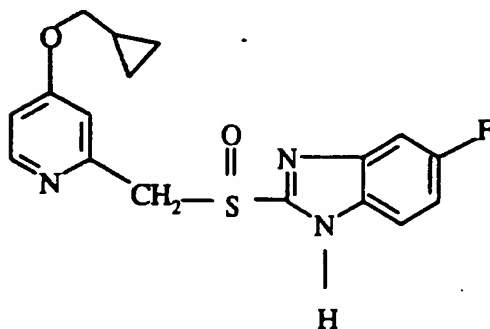
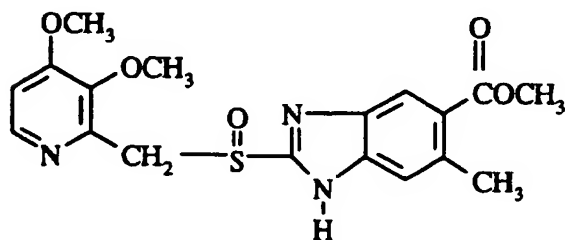
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moities thereof may be branched and straight C₁-C₉ -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

5

Examples of proton pump inhibitors according to formula I are

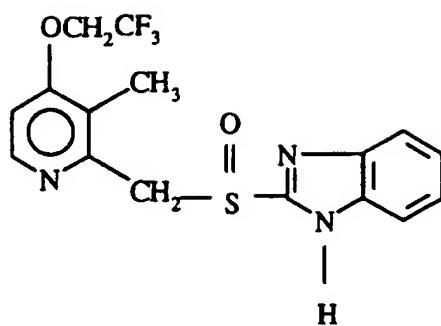


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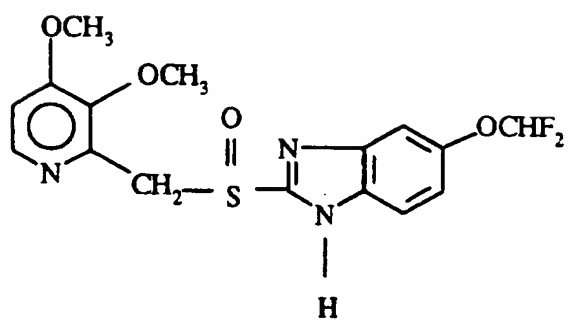


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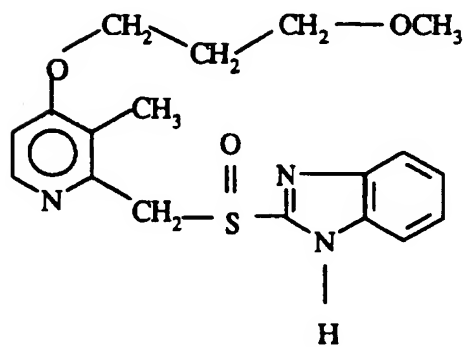


Lansoprazole



Pantoprazole

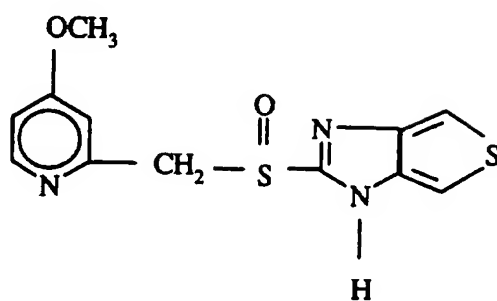
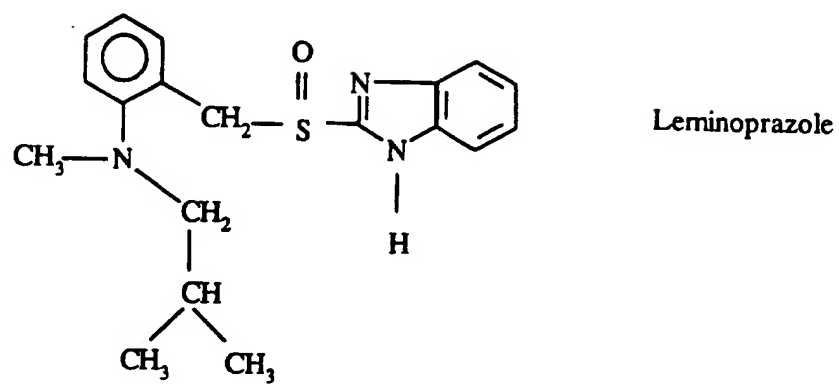
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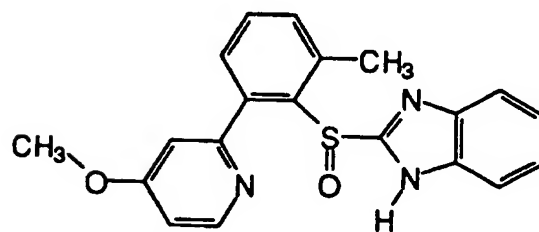
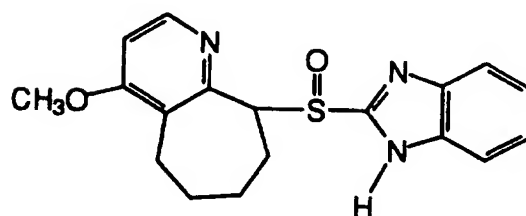
Pariprazole

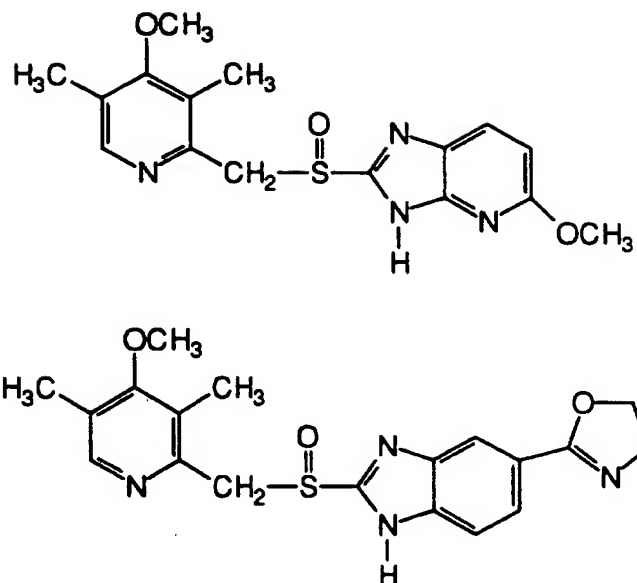
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5 The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the racemates or the single enantiomers.

10

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO94/27988 and WO95/01977.

15

These proton pump inhibitors are, as already mentioned, useful for inhibiting gastric acid secretion in mammals and man. In a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, they may be
20 used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is

desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of *Helicobacter* infections and diseases related to these.

These proton pump inhibitors are, however, susceptible to degradation/transformation in acidic reacting and neutral media. The degradation is catalyzed by acidic reacting compounds and the proton pump inhibitors are usually stabilized in mixtures with alkaline reacting compounds.

In respect to the stability properties of the proton pump inhibitors mentioned above, it is obvious that a proton pump inhibitor in an oral solid dosage form must be protected from contact with the acidic reacting gastric juice and the active substance must be transferred in intact form to that part of the gastrointestinal tract where pH is less acidic, neutral or alkaline and where rapid absorption of the pharmaceutically active substance, i.e. the proton pump inhibitor, can occur.

A pharmaceutical dosage form of these proton pump inhibitors is best protected from contact with acidic gastric juice by an enteric coating layer. In US-A 4,853,230 such enteric coated preparations of different acid labile substances are described. Said preparations contain an alkaline core material comprising the active substance, a separating layer and an enteric coating layer.

Ordinary enteric coating layers, however, comprise compounds which contain acidic groups. If covered with such an enteric coating layer, the acid labile substance may rapidly decompose by direct or indirect contact with the acidic groups resulting in discoloration of the content and loss in content of the active compound with the passage of time. The discoloration can be avoided by applying some type of separating layer between the core material comprising the susceptible proton pump inhibitor and the enteric coating layer.

Thus, there are a lot of patent applications describing such a separating layer between a core material comprising the pharmaceutically active substance and an enteric coating layer. See for instance, US-A 4,786,505, EP 0,277,741 and EP 0,342,522. The prior art techniques to
5 apply at least two different layers on a pellet core or a tablet comprising an acid labile compound is rather complicated and there is a demand for finding new processes and formulations to simplify the manufacturing of such enteric coated articles comprising acid labile substances.

10 Summary of the invention.

According to one aspect of the invention a new pharmaceutical dosage form is provided in the form of an enteric coated tablet. Alternatively, individually enteric coated units are prepared and filled into a capsule, a sachet or included in a tableted multiple unit dosage
15 form.

The present invention is characterized by the presence of a separating layer between an alkaline reacting core material comprising a pharmaceutically active acid labile substance and an enteric coating layer, wherein the separating layer comprises a water soluble salt of
20 an enteric coating polymer.

According to a second aspect the present invention provides a process for the manufacture of two functionally different layers in one manufacturing step. By such a process a separating layer comprising a water soluble salt of an enteric coating polymer is obtained,
25 as well as the enteric coating layer itself.

Thus, the present invention simplifies the preparation of enteric coated articles comprising a separating layer between a core material and an enteric coating layer by providing a new process for the manufacture of such dosage forms. According to said process the separating
30 layer is formed by an in situ reaction between the enteric coating polymer and the alkaline core material comprising the pharmaceutically active substance.

Brief description of the Figures

Figure 1 is a photo showing a cross-section of a tablet manufactured according to the
5 invention described in the present specification.

Figure 2 is a schematic drawing of the photo disclosed in Figure 1. The tablet has an enteric
coating layer (3), which has been applied on an alkaline core material (1) comprising the
pharmaceutically active substance. Between the enteric coating layer (3) and the core
10 material (1) there is a separating layer (2) shown. The separating layer (2) is on the photo
inked by a fluorescent colour.

Detailed description of the invention

15 One object of the present invention is to provide a new enteric coated pharmaceutical
formulation comprising a core material that contains a proton pump inhibitor, one or more
alkaline reacting compound(s) and optionally pharmaceutically acceptable excipients, which
formulation has a water soluble separating layer and an enteric coating layer and wherein
the core material is alkaline and the separating layer is being formed in situ during the
20 enteric coating as a salt between the enteric coating polymer(s) and an alkaline reacting
compound(s) in the core material.

Another object of the present invention is to provide a new process for the manufacture of
such enteric coated pharmaceutical formulations comprising a core material of a proton
25 pump inhibitor wherein a separating layer is formed in situ during the enteric coating by a
reaction between the enteric coating polymer(s) and one or more alkaline reacting
compound(s) in the core material, i.e. thereby a salt is formed between the enteric coating
polymer(s) and the alkaline reacting compound(s).

30 The new pharmaceutical dosage form according to the invention is further characterized in
the following way. Compacted tablets or individual cores (in the form of small tablets, small

beads, granules or pellets) contain the proton pump inhibitor in the form of a racemate or one of its single enantiomers or an alkaline salt of said compound or one of its single enantiomers. The tablets or individual cores, that also comprise one or more alkaline reacting compound(s) which is in the position to form a water soluble salt by a reaction with an enteric coating material, are coated with one or more enteric coating layers.

The separating layer is formed in situ by a reaction between the enteric coating polymer(s) and the alkaline reacting compound(s) in the core material during the enteric coating process.

10

The core material for the manufacture of enteric coated pellets can be prepared according to two main principles. Firstly, seeds can be layered with the proton pump inhibitor, alkaline reacting compound(s) and necessary excipients to give an alkaline reacting core material, or the alkaline reacting core material can be prepared as substantially homogeneous cores or tablets comprising the proton pump inhibitor and the alkaline reacting compound(s).

The alkaline reacting compound(s) in the core material or tablet cores, necessary for an in situ reaction with the enteric coating polymer, is a substance in the position to form a water soluble salt with an enteric coating polymer. Such alkaline reacting compounds are for instance amino acids, such as lysine, arginine, ornithine, histidine, organic buffering compounds such as trometamine (i.e. Tris-buffer), N-amino sugars such as N-methyl-D-glucamine (i.e. Meglumine), N-ethyl-D-glucamine (i.e. Eglumine), glucosamine, disodium-N-stearoyl-glutamate, heterocyclic amine derivatives such as piperazine or its hexahydrate, N-methylpiperazine, morpholine, 1-(2-hydroxyethyl)pyrrolidine, alkali salts of citric acid, tartaric acid, caproic acid or fatty acids, alkali metal phosphates, silicates or carbonates, sodium, potassium, magnesium, calcium or aluminium hydroxides and organic amines such as ethylamine, dicyclohexylamine or triethanolamine, or alkaline ammonium salts.

The core material as such should be an alkaline reacting core material, i.e. the amount of alkaline reacting compound(s) available in the core material should be enough to form a salt between the enteric coating polymer(s) and the alkaline reacting compound(s).

Thus, the concentration of alkaline reacting compound(s) in the core material (before applying the enteric coating polymer) is from approximately 0.1 mmol/g dry ingredients in the alkali containing part of the core material up to approximately 15 mmol/g, preferably the concentration shall be more than 0.3 mmol/g dry ingredients in the alkaline part of the core material.

The upper limit range is only restricted by the need to include a pharmaceutically active ingredient and excipients such as binders etc in the alkaline core material. The concentration of alkaline reacting compound(s) may be illustrated as follows. For a core material where, for instance, 10 % w/w of a proton pump inhibitor and 5 % w/w of excipients (binders, surfactants etc) are to be included, 85 % w/w remains to possible disposition to the alkaline reacting compound(s). For such a core material, this means that, if the alkaline reacting compound is sodium bicarbonate which has the rather low molecular weight of 84 u, the concentration of the alkaline material in the core material will be $[(85/84)/100] \times 1\,000$, i.e. approximately 9.9 mmol/g in the alkali containing part/layer.

One or more enteric coating layers are applied onto the prepared core material or tablets by using a suitable aqueous coating technique. The enteric coating material is dispersed and/or dissolved in an aqueous vehicle. As enteric coating polymer(s) one or more, separately or in combination, of the following can be used; methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layer(s) may contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties, such as flexibility and hardness of the enteric coating layer(s). The amount of plasticizer is optimized for each enteric coating formulation, in relation to selected enteric coating polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). The mechanical properties of the enteric coating are especially important for a tableted multiple unit dosage form, i.e. the individually enteric coated units must withstand

the compression into a tableted multiple unit dosage form without any significant effect on the acid resistance. Suitable plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

5

The preparation of the core material containing the proton pump inhibitor and alkaline reacting compound(s) is described more in detail below. The individually enteric coated cores can be constituted according to different principles.

10 The active substance, the proton pump inhibitor, used as a racemate or one of its single enantiomers or an alkaline salt of said compound or one of its single enantiomers, mixed with the alkaline reacting compound(s) is applied on seeds and are used for further processing.

15 The seeds, which are to be layered with the active substances, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise active substance in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for
20 the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Before the seeds are layered, the active substance is mixed with alkaline reacting
25 compound(s) and further components to obtain preferred handling and processing properties and suitable concentration of the active substance. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used. Binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethylcellulose
30 sodium, polyvinylpyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of

pharmaceutically acceptable non-ionic or ionic surfactants such as a for instance sodium lauryl sulfate or polysorbates.

Alternatively, the active substance mixed with alkaline compound(s) and further mixed with
5 suitable constituents can be formulated into tablets or individual cores. Said tablets or cores
may be produced by compression/extrusion/spheronization or balling utilizing different
processing equipments. The manufactured tablets or cores can further be layered with
additional ingredients comprising active substance and alkaline reacting compound(s) and/or
be used for further processing.

10

The active substance may optionally be mixed with alkaline pharmaceutically acceptable
substance (or substances) for further stabilisation. Such substances can be chosen among,
but are not restricted to, substances such as for instance the above mentioned alkaline
reacting compounds or other alkaline reacting substances known by the skilled person in the
15 art to be useful as stabilizers for acidic susceptible substances.

Alternatively, the aforementioned alkaline reacting core material can be prepared by the use
of spray drying or spray congealing technique.

20 The prepared alkaline reacting core material in the form of tablets or pellets are spray
coated with an aqueous enteric coating polymer dispersion/solution. The process
parameters such as inlet air temperature, air flow, atomizer air flow and spraying rate are
adjusted with respect to the equipment used for the process as well as the specific enteric
coating polymer(s). The inlet air temperature must not be such that the enteric coating
25 polymer(s) will block in the spraying nozzles.

The invention is described more in detail by the following examples, which are not intended
to limit the scope of the invention.

Example 1

Tablets containing lansoprazole and arginine are produced according to the following procedure. Firstly, dry ingredients are thoroughly mixed and then granulated with a solution
5 in a laboratory mixer. The dried granules are mixed with lubricants etc. in a final mixing step.

| <u>Dry ingredients for granulation</u> (for approx. 4000 tablets) | <u>Concentration</u> (mmol/g dry ingredients in the alkaline tablet core) |
|-------------------------------------------------------------------|---------------------------------------------------------------------------------|
|-------------------------------------------------------------------|---------------------------------------------------------------------------------|

10

| | | |
|-------------------------------|---------|-----|
| Lansoprazole | 40.4 g | |
| L-arginine (passing 120 mesh) | 365.4 g | 4.2 |
| Microcrystalline cellulose | 38.5 g | |

15

Granulating solution

| | |
|-----------------|-------|
| Distilled water | 173 g |
| Corn starch | 7.7 g |

20 The solution is poured over the premixed powder mass during mixing. The wet granules are dried on a tray in a drying cabinet. The dried granules are milled to pass a 1.0 mm sieve. The granules are mixed with

| | |
|----------------------------|--------|
| Talc | 3.1 g |
| 25 Sodium dodecyl sulphate | 20.8 g |
| Microcrystalline cellulose | 19.2 g |
| Magnesium stearate | 5.0 g |

in a laboratory mixer, and then compressed into tablets having a size of 7 mm Ø and a
30 weight of approximately 125 mg. The obtained tablets have a content of lansoprazole of 10 mg per tablet.

Obtained tablets are spray coated with the enteric coating dispersion defined below, in a Wurster equipped fluidized bed.

5 Enteric coating dispersion

| | |
|------------------------------|--------|
| Water | 80.0 g |
| Triethylcitrate | 1.3 g |
| Na-laurylsulphate | 0.2 g |
| Hydroxypropylmethylcellulose | |
| 10 acetate succinate LF | 6.3 g |
| Talc | 1.9 g |

This single coating step resulted in tablets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in
15 water. Figure 1, obtained with confocal laser scanning microscopy (CLSM) shows a cross-section of the tablet where the separating layer is easily detected as a layer having an intense fluorescence.

The separating layer is spontaneously formed in situ during the process, as a salt between
20 the alkaline reacting compound and the enteric coating polymer.

Example 2

Core material containing the magnesium salt of (-)-omeprazole and the alkaline reacting
25 compound trometamine (= tris-buffer) is prepared by extrusion and spheronization.

The powder mass is mixed in a laboratory mixer and then water is added.

| <u>Powder mixture</u> | | <u>Concentration</u> (mmol/g dry ingredients in the alkaline core material) |
|-----------------------|-------------------------------------|-----------------------------------------------------------------------------------|
| 5 | Magnesium salt of (-)-omeprazole | 400 g |
| | Microcrystalline cellulose | 300 g |
| | Trometamine | 1000 g 4.1 |
| | PVP-XL | 100 g |
| | Mannitol pwd | 195 g |
| 10 | Hydroxypropyl methylcellulose 6 cps | 5 g |
| | Water | q.s. |

The powder mixture is mixed with the water and the wet mass is mixed to obtain a suitable consistency of the mass.

15

Extrusion is performed with an extruder fitted with 1.0 mm screen. The extrudate is formed into pellets on a spheronizer and dried in a fluidized bed drier.

200 g of the obtained pellets are spray coated with the enteric coating dispersion described
20 below, in a Wurster equipped fluidized bed.

Enteric coating dispersion

| | | |
|----|--------------------------------|---------|
| | Water | 93.9 g |
| | Polyethylene glycol 400 | 4.6 g |
| 25 | Eudragit TM L30D-55 | 151.5 g |

This single coating step resulted in pellets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt
30 between the alkaline reacting compound and the enteric coating polymer.

Enteric coated pellets having a separating layer are obtained. These pellets may be filled in capsules or sachets for oral administration.

5 Example 3

Core material containing omeprazole and N-methyl-D-glucamine (=meglumine) is prepared by extrusion and spheronization of the below described composition using the same procedure as in Example 2;

10

Powder mixture

Concentration

(mmol/g dry ingredients in
the alkaline core material)

| | | | |
|----|----------------------------|---------|-----|
| 15 | Omeprazole | 100.0 g | |
| | Microcrystalline cellulose | 50.0 g | |
| | Meglumine | 500.0 g | 2.6 |
| | Mannitol pwd | 297.0 g | |
| | Sodium starch glycolate | 48.0 g | |
| 20 | Sodium laurylsulphate | 5.0 g | |
| | Water | q.s. | |

Obtained dried pellets/cores are spray coated with the enteric coating dispersion described below, in a Wurster equipped fluidized bed.

25

Enteric coating dispersion

| | | |
|--|-------------------------------|---------|
| | Water | 93.9 g |
| | Polyethylene glycol 400 | 4.6 g |
| | Eudragit [™] L30D-55 | 151.5 g |

30

This single coating step resulted in tablets having two polymeric layers with different characteristics. The inner layer is not soluble in acetone, as the outer one, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

5

The obtained pellets having a separating layer and an enteric coating layer, are suitable for filling into hard gelatine capsules or sachets for oral administration.

Example 4

10

Core material containing magnesium salt of omeprazole and N-methyl-D-glucamine (meglumine) is prepared by layer coating in a Wurster equipped fluidized bed on sugar seeds. For this operation the following materials are used;

| 15 | <u>Substance</u> | <u>Amount</u> | <u>Concentration</u> |
|----|------------------------------|---------------|------------------------------------------------------------|
| | | | (mmol/g dry ingredients in the alkali containing layer) |
| | Water purified | 102 g | |
| | Ethanol 99% (w/v) | 102 g | |
| 20 | HPMC 6 cps | 2 g | |
| | N-methyl-D-glucamine | 3.3 g | 0.37 |
| | Magnesium salt of omeprazole | 40 g | |
| | Non Pareille | 500 g | |

25 First the water and ethanol were mixed whereafter the HPMC was dissolved in the obtained solution. N-methyl-D-glucamine and magnesium salt of omeprazole were dissolved/suspended in the solution. The sugar cores (Non Pareille) were used as starting seeds for the formation of core material. A peristaltic pump was used to feed the spraying suspension, which was fed with a velocity of 3.9 g/min.

30

The Wurster apparatus was equipped with a 60 mm high insertion tube, having a diameter of 50 mm, positioned to leave a 10 mm slit below it. A spraying nozzle having a 0.8 mm opening was used. The atomizing air flow was 2.3 Nm³/h and air pressure used was 1.9 bar. The inlet air temperature was 50° C and flow used 43 m³/h.

5

After the core formation step, 100 grams of the obtained core material was film-coated by spraying with an enteric coating dispersion as described below, using the same equipment as in the core formation step.

10 Enteric coating dispersion

| | | |
|----|-------------------------------|--------|
| | Water purified | 183 g |
| | Triethyl citrate | 2.9 g |
| | Sodium laurylsulphate | 0.4 g |
| 15 | Hydroxypropyl methylcellulose | |
| | acetate succinate LF | 14.4 g |
| | Talc | 4.3 g |

First the triethyl citrate was dissolved in the water, and thereafter the sodium laurylsulphate was added. The hydroxypropylmethylcellulose acetate succinate was dispersed in the solution, and then the talc was added. The dispersion was fed with a rate of 3.8 g/min.

20

Inlet air temperature used was 42 ° C and flow was set to 40 Nm³/h. Atomizing air flow used was 2.1 Nm³/h , obtained with a pressure of 1.7 bar.

25

After finalizing the spraying, the inlet air temperature is rised to 60° C and the product is kept at this temperature for appr. 5 minutes.

This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but

30

soluble in water. Using confocal laser scanning microscopy to study a cross-section of the cores from this example, the presence of an inner layer was confirmed.

The separating layer is spontaneously formed in situ during the process, as a salt between
5 the alkaline reacting compound and the enteric coating polymer.

Example 5

A rotogranulator was used to produce spherical core units containing pantoprazole. As
10 starting material inert sugar seeds (Non-Pareille) with an average size between 0.6 to 0.71 mm Ø was used. The sugar seeds were coating layered with the powder mixture described below, by spraying a 5 % solution of HPMC 6 cps in water.

The obtained core material containing pantoprazole was dried at 40°C for 16 hours in
15 vacuum and then sieved to give granules between 0.6 mm to 1.25 mm Ø .

Starting material

Non-Pareille 110 parts by weight

| 20 | <u>Powder mixture</u> | <u>Amount</u> | <u>Concentration</u> |
|----|----------------------------|----------------------|---------------------------------------------------------|
| | | | (mmol/g dry ingredients in the alkali containing layer) |
| | Pantoprazole | 29.3 parts by weight | |
| 25 | L-Lysine | 22.0 " | 0.88 |
| | Sucrose | 36.7 " | |
| | Corn starch | 42.5 " | |
| | Microcrystalline cellulose | 36.7 " | |

Solution

Hydroxypropyl methylcellulose 2.9 "

Water (58.7 ")

- 5 250 g of the core material produced in this way was spray coated with an enteric coating dispersion in a Wurster equipped fluidized bed apparatus. The dispersion was made by adding the mentioned ingredients in stated order, while stirring.

Dispersion

| | | |
|----|------------------------------|---------|
| 10 | Water | 626.8 g |
| | Triethylcitrate | 9.8 g |
| | Sodium-laurylsulphate | 1.5 g |
| | Hydroxypropylmethylcellulose | |
| | acetate succinate LF | 49.2 g |
| 15 | Talc | 14.8 g |

Enteric coated pellets having a water soluble separating layer were obtained. These pellets may be filled in capsules or sachets for oral administration.

20 Example 6

Omeprazole tablets, 6 mm in diameter containing 20 mg of omeprazole were prepared by mixing and granulating dry powder ingredients with water in a Kenwood mixer. For this operation the following materials are used;

| | <u>Substance</u> | <u>Amount</u> | <u>Concentration</u> |
|----|----------------------------------------|---------------|---------------------------------------------------------|
| | | | (mmol/g dry ingredients in the alkaline tablet core) |
| | Omeprazole | 40.0 g | |
| 5 | Mannitol pwd | 68.0 g | |
| | Microcrystalline cellulose | 35.0 g | |
| | Polyvinylpyrrolidone cross-linked | 30.0 g | |
| | Hydroxypropylcellulose low-substituted | 20.0 g | |
| | L-arginine | 5.3 g | 0.14 |
| 10 | Sodium laurylsulphate | 2.0 g | |
| | Water purified q.s. | approx 50 g | |
| | Sodium stearyl fumarate (SSF) | 1.0 g | |

The dry powders except for SSF were mixed to homogeneity. This mixture was moistened
15 with the water and the wet mass dried on a tray in a drying oven. The obtained granules
were milled to pass a screen with 0.8 mm apertures. Then the lubricant SSF was mixed with
the granules using the same Kenwood mixer as before.

Cores having an average weight of 101 mg were compressed on a tableting machine
20 equipped with 6mm diameter punches.

After the core formation step, 50 grams of the obtained cores were film-coated by spraying
an aqueous enteric coating dispersion as described below, using a Wurster equipped
fluidized bed.

Enteric coating dispersion

| <u>Substance</u> | <u>Amount</u> |
|------------------------------|---------------|
| Water purified | 183 g |
| Triethyl citrate | 2.9 g |
| 5 Sodium laurylsulphate | 0.4 g |
| Hydroxypropylmethylcellulose | |
| acetate succinate LF | 14.4 g |
| Talc | 4.3 g |

10

This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water.

- 15 The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

Example 7

- 20 Tablets, 7 mm in diameter containing omeprazole and disodiumhydrogenphosphate was prepared by mixing and granulating dry powder ingredients with a water solution containing sodium laurylsulphate, in a Kenwood mixer. For this operation the following materials are used:

25

24

| | <u>Substance</u> | <u>Amount</u> | <u>Concentration</u> |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------------------------------------------------------|
| | | | (mmol/g dry ingredients in the alkaline tablet core) |
| | Omeprazole | 80 g | |
| 5 | Mannitol pwd | 88 g | |
| | Microcrystalline cellulose | 132 g | |
| | L-HPC | 53 g | |
| | Disodiumhydrogenphosphate dihydrate | 104 g | 1.12 |
| 10 | <u>Granulation liquid</u> | | |
| | Water purified | 80 g | |
| | Sodium laurylsulphate | 3 g | |
| | Water purified q.s. | | |
| 15 | <u>Final mixing</u> | | |
| | Sodium stearyl fumarate (SSF) | 10 g | |
| | Polyvinylpyrrolidone crosslinked | 50 g | |
| 20 | The dry powders except for SSF were mixed to homogeneity. This mixture was moistened first with the granulation liquid and then with water until satisfactory consistency of the mass. The wet mass was dried on a tray in a drying oven. The obtained granules were milled to pass a screen with 0.8 mm apertures and then the lubricant SSF and the disintegrating agent polyvinylpyrrolidone crosslinked were mixed with the obtained granules using the | | |
| 25 | same Kenwood mixer as before. | | |

Cores having an average weight of 130 mg were compressed on a tableting machine equipped with 7 mm diameter punches.

After the core formation step, 50 grams of the obtained cores were film-coated by spraying with an aqueous enteric coating dispersion as described below, using a Wurster equipped fluidized bed.

5 Enteric coating dispersion

| | | |
|----|-------------------------------|--------|
| | Water purified | 183 g |
| | Triethyl citrate | 2.9 g |
| | Sodium laurylsulphate | 0.4 g |
| 10 | Hydroxypropyl methylcellulose | |
| | acetate succinate LF | 14.4 g |
| | Talc | 4.3 g |

15 This single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the inorganic alkaline reacting compound and the enteric coating polymer.

Reference Examples 1 and 2

20

Placebo tablets, 6 mm in diameter was prepared by mixing and granulating dry powder ingredients with water in a Kenwood mixer. For this operation the following materials are used;

| | <u>Substance</u> | <u>Amount</u> | <u>Concentration</u> (mmol/g dry ingredients in the alkali containing layer) | |
|---|-----------------------------------------------------|---------------|------------------------------------------------------------------------------------|------------|
| | | | Ref.Ex. 1 | Ref.Ex. 2 |
| 5 | Mannitol pwd | 161.5 g | 141.3 g | |
| | Microcrystalline cellulose | 38.5 g | 38.5 g | |
| | Na ₂ HPO ₄ ·2H ₂ O | ----- | 20.2 g | ----- 0.56 |
| | Water purified q.s. approx | 45 g | 45 g | |
| | Sodium stearyl fumarate (SSF) | 1.0 g | 1.0 g | |

10

The dry powders except for SSF were mixed to homogeneity. This mixture was moistened with the water and the wet mass dried on a tray in a drying oven. The obtained granules were milled to pass a screen with 0.8 mm apertures. Then the lubricant SSF was mixed with the granules using the same Kenwood mixer as before.

15

Cores having an average weight of 93- 94 mg were compressed on a tableting machine equipped with 6 mm diameter punches.

After the core formation step, 50 grams of each kind of the obtained cores were (separately) film-coated by spraying an aqueous enteric coating dispersion according to below, using a Wurster equipped fluidized bed.

| <u>Enteric coating dispersion</u> | |
|---------------------------------------------------|---------------|
| <u>Substance</u> | <u>Amount</u> |
| 25 Water purified | 183 g |
| Triethyl citrate | 2.9 g |
| Sodium laurylsulphate | 0.4 g |
| Hydroxypropylmethylcellulose acetate succinate LF | 14.4 g |
| 30 Talc | 4.3 g |

These reference examples show that presence of the alkaline material in the core material composition is necessary for the formation of an in situ formed spontaneously developed separating layer.

5

For Reference Ex. 1, this single film-coating step resulted in cores having only one coating layer, being soluble in acetone. No separating layer was spontaneously formed.

10 For Reference Ex. 2, this single film-coating step resulted in cores having two polymeric coating layers with different characteristics. The inner layer is not soluble in acetone, as the outer layer, but soluble in water. The separating layer is spontaneously formed in situ during the process, as a salt between the alkaline reacting compound and the enteric coating polymer.

15 By using confocal laser scanning microscopy to study a cross-section of the cores from the Reference example 2, the presence of an inner layer was confirmed. In contrast, examining a cross-section of a core from Reference example 1, no inner layer was seen.

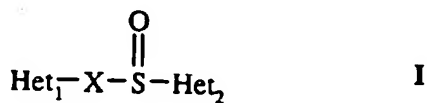
20 The best mode to practice the invention is by the formulations described in Examples 1 and 2.

The different active substances, i.e. proton pump inhibitors, are prepared according to information disclosed in the Patent specifications mentioned in page 6 of this specification.

Claims

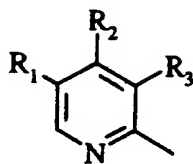
1. An oral pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline reacting compound(s) and optionally pharmaceutically acceptable excipients having a water soluble separating layer and an enteric coating layer characterized in that the core material is alkaline reacting and that the separating layer is being formed in situ during the enteric coating as a water soluble salt between the enteric coating layer polymer(s) and the alkaline reacting compound(s).
2. A dosage form according to claim 1, wherein the alkaline reacting compounds are selected from the group of alkaline organic substances, hydroxides of alkali metals or one of their alkaline salts of phosphoric acid, carbonic acid or silicic acid, or an alkaline ammonium salt.
3. A dosage form according to claim 2, wherein the alkaline reacting substance is a hydroxide of an alkali metal or an alkaline salt of phosphoric acid, carbonic acid or silicic acid, or an alkaline ammonium salt.
4. A dosage form according to claim 2, wherein the alkaline reacting compound is an alkaline organic substance, e.g. an amino acid or a salt thereof, an alkaline amine or a derivative thereof, or an alkaline salt of a weak organic acid.
5. A dosage form according to claim 2, wherein the alkaline organic substance is an amino acid, e.g. lysine, arginine, ornithine or histidine, or an alkaline amine or a derivative thereof, e.g. N-methyl-D-glucamine or trometamine.
6. A dosage form according to claim 1, wherein the alkaline reacting compounds are present in a concentration of more than 0.1 mmol/g dry ingredients in the alkaline part of the core material.

7. A dosage form according to claim 1, wherein the enteric coating polymer(s) is/are hydroxypropyl cellulose derivative(s), e.g. hydroxypropylmethylcellulose acetate succinate.
8. A dosage form according to claim 1, wherein the enteric coating polymer is copolymerized methacrylic acid/methacrylic acid methyl esters.
9. A dosage form according to claim 1, wherein the proton pump inhibitor is a compound of the general formula I or a pharmaceutically acceptable salt thereof or a pure enantiomer thereof in neutral form or in the form of an alkaline salt

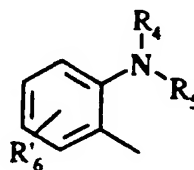


wherein

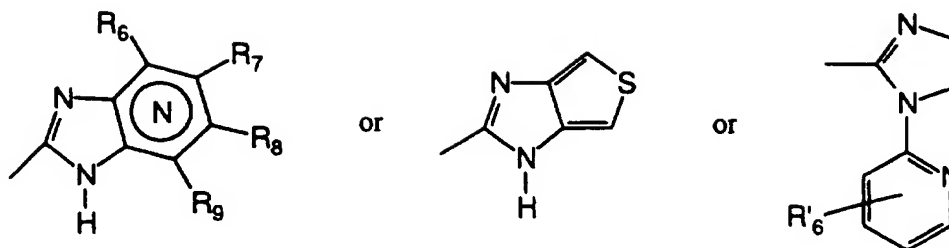
Het₁ is



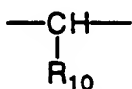
or



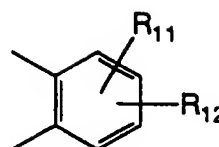
30

Het₂ is

X =



or



5 wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

- 10 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

15

R'₆ is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

20

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl and alkyl groups, alkoxy groups and moities thereof may be branched and straight C₁-C₉ -chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

5

10. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole or an alkaline salt thereof.

11. A dosage form according to claim 1, wherein the proton pump inhibitor is a pure
10 enantiomer of omeprazole or an alkaline salt thereof.

12. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its pure enantiomers or a pharmaceutically acceptable salt thereof.

13. A dosage form according to claim 1, wherein the proton pump inhibitor is
15 pantoprazole, one of its pure enantiomers or a pharmaceutically acceptable salt thereof.

14. A dosage form according to claim 1, wherein the alkaline reacting core material is individual pellets intended for a capsule formulation or a tableted multiple unit dosage
20 form.

15. A dosage form according to claim 1, wherein the alkaline reacting core material is a tablet.

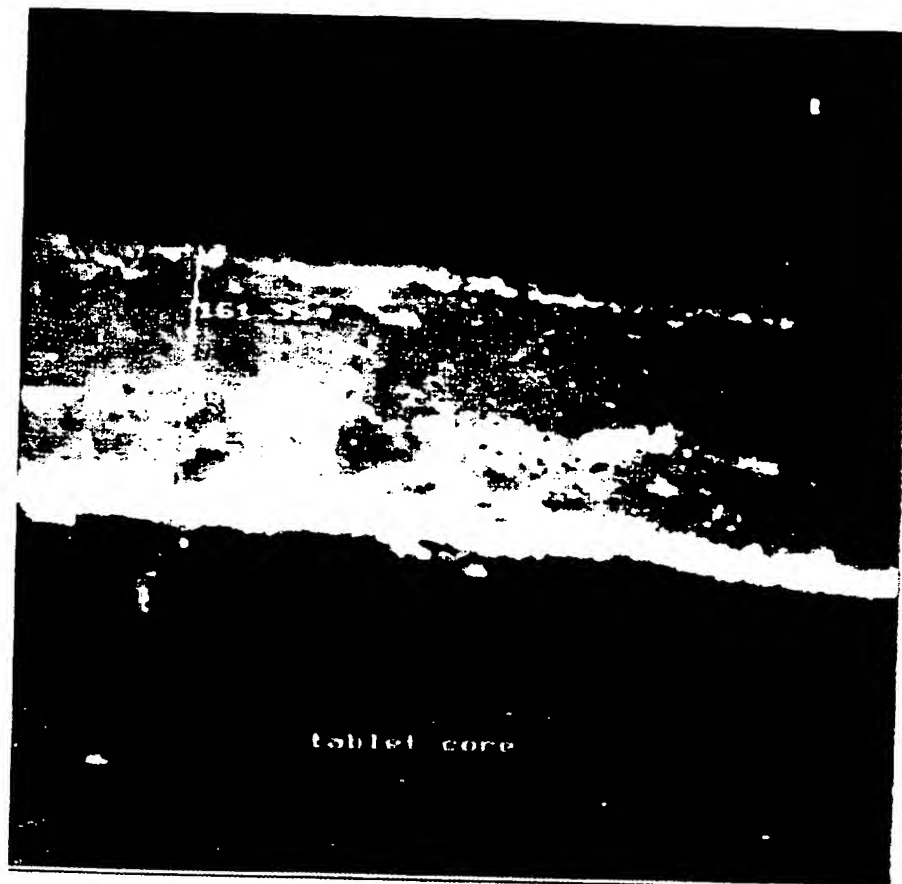
16. A dosage form according to claim 1, wherein individually enteric coated pellets are
25 compressed into a tableted multiple unit dosage form.

17. A process for the preparation of an oral, enteric coated pharmaceutical dosage form comprising a core material that contains a proton pump inhibitor, one or more alkaline
30 reacting compounds and optionally pharmaceutically acceptable excipients having a water

soluble separating layer and an enteric coating layer characterized in that an alkaline reacting core material is prepared and coated with an enteric coating polymer wherein a separating layer between the core material and the enteric coating layer is formed in situ by a reaction between the enteric coating polymer(s) and the alkaline reacting compound(s) in the core material during the application of the enteric coating onto the alkaline reacting core material.

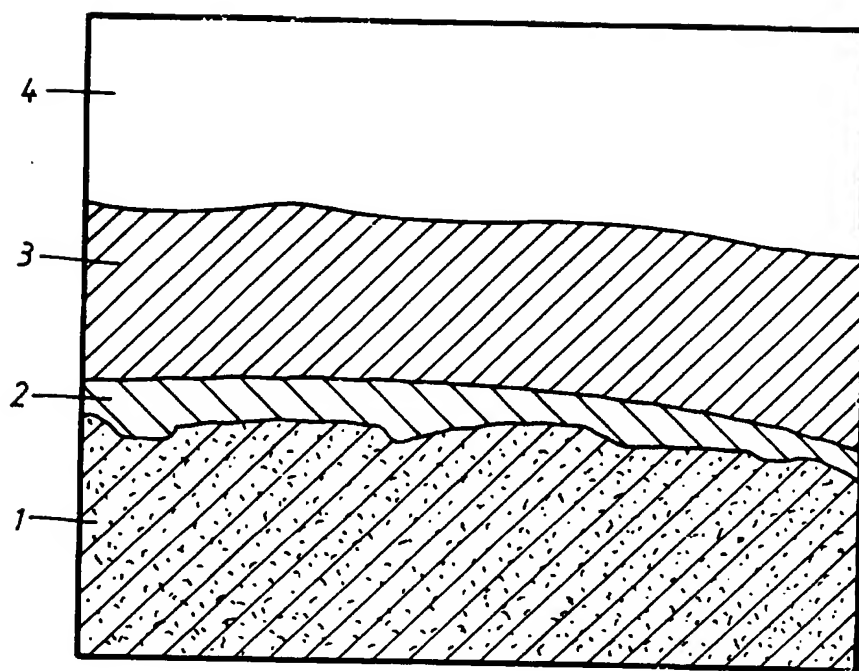
18. An oral, pharmaceutical dosage form comprising a proton pump inhibitor as defined in any of claims 1-16 for use in inhibiting gastric acid secretion in mammals and man.
19. A method for inhibiting gastric acid secretion in mammals and man by administering to a host in need thereof a dosage form comprising a therapeutically effective dose of a proton pump inhibitor as defined in any of claims 1-16.
20. Use of an oral pharmaceutical dosage form defined in any of claims 1 - 16 for the manufacture of a medicament useful in the treatment of gastric acid related diseases.

Fig. 1



2 / 2

Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/00161

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/30, A61K 31/44, A61K 47/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, USFULLTEXT, CAPLUS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) -- | 1-18,20 |
| A | Dialog Information Services, File 351, Word Patent Index 81-95, Dialog accession no. 009584650, WPI accession no. 93-278196/35, Yoshitomi Pharm Ind KK: "Anti-ulcer agent- contains benzimidazole cpd., amino acid and buffer, giving good stability", JP 5194225, A, 930803, 9335 (Basic) -- | 1-18,20 |
| A | EP 0365947 A1 (PHARMACIA AB), 2 May 1990 (02.05.90) -- ----- | 1-18,20 |

☐ Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 May 1996

Date of mailing of the international search report

10-05-1996

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INTERNATIONAL SEARCH REPORT

Inte: onal application No.

PCT/SE 96/00161

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

01/04/96

International application No.

PCT/SE 96/00161

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| EP-A2- 0247983 | 02/12/87 | SE-T3- 0247983 | |
| | | AR-A- 240250 | 30/03/90 |
| | | AU-B,B- 601974 | 27/09/90 |
| | | AU-A- 7191287 | 05/11/87 |
| | | CA-A- 1292693 | 03/12/91 |
| | | DE-A- 3783394 | 18/02/93 |
| | | DK-B- 169988 | 24/04/95 |
| | | EP-A,A,A 0496437 | 29/07/92 |
| | | EP-A,A- 0567201 | 27/10/93 |
| | | ES-T- 2006457 | 01/01/94 |
| | | GB-A- 2189698 | 04/11/87 |
| | | HK-A- 135294 | 09/12/94 |
| | | HR-A- 920854 | 31/10/94 |
| | | IE-B- 61416 | 02/11/94 |
| | | JP-C- 1863556 | 08/08/94 |
| | | JP-A- 5294831 | 09/11/93 |
| | | JP-A- 62258320 | 10/11/87 |
| | | LT-A- 1683 | 25/07/95 |
| | | LT-B- 3699 | 26/02/96 |
| | | NO-B,C- 174239 | 27/12/93 |
| | | SG-A- 154294 | 17/03/95 |
| | | SU-A- 1820837 | 07/06/93 |
| | | US-A- 4786505 | 22/11/88 |
| <hr/> | | | |
| EP-A1- 0365947 | 02/05/90 | SE-T3- 0365947 | |
| | | AU-B,B- 612525 | 11/07/91 |
| | | AU-A- 4365089 | 03/05/90 |
| | | CA-A- 2000932 | 26/04/90 |
| | | DE-T- 68907177 | 13/01/94 |
| | | ES-T- 2055775 | 01/09/94 |
| | | HK-A- 123394 | 18/11/94 |
| | | IE-B- 62640 | 22/02/95 |
| | | JP-A- 2164821 | 25/06/90 |
| | | LV-B- 10382 | 20/12/95 |
| | | PT-B- 92103 | 09/08/95 |
| | | SE-A- 8803822 | 26/10/88 |
| | | SG-A- 123894 | 17/03/95 |
| | | US-A- 5178868 | 12/01/93 |
| <hr/> | | | |